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Xenobiotic metabolizing gene variants and renal cell cancer: a multicenter study

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Background: The countries of Central and Eastern Europe have among the highest worldwide rates of renal cell cancer (RCC). Few studies have examined whether genetic variation in xenobiotic metabolic pathway genes may modify risk for this cancer. **Methods:** The Central and Eastern Europe Renal Cell Cancer study was a hospital-based case–control study conducted between 1998 and 2003 across seven centers in Central and Eastern Europe. Detailed data were collected from 874 cases and 2053 controls on demographics, work history, and occupational exposure to chemical agents. Genes [cytochrome P-450 family, *N*-acetyltransferases, NAD(P)H:quinone oxidoreductase I (*NQO1*), microsomal epoxide hydrolase (*mEH*), catechol-*O*-methyltransferase (*COMT*), uridine diphosphate-glucuronosyltransferase (*UGT*)] were selected for the present analysis based on their putative role in xenobiotic metabolism. Haplotypes were calculated using fastPhase. Odds ratios and 95% confidence intervals were estimated by unconditional logistic regression adjusted for country of residence, age, sex, smoking, alcohol intake, obesity, and hypertension. **Results:** We observed an increased risk of RCC with one SNP. After adjustment for multiple comparisons it did not remain significant. Neither *NAT1* nor *NAT2* slow acetylation was associated with disease. **Conclusion:** We observed no association between this pathway and renal cell cancer.

Keywords: renal cell cancer, epidemiology, *NAT1, NAT2, CYP, NQO1, mEH, COMT*

INTRODUCTION

Globally, there are 210,000 cases and 100,000 deaths each year from kidney cancer. The countries of Central and Eastern Europe have among the highest worldwide rates of this disease, particularly the Czech Republic, which has an incidence of 23.6/100,000 among men and 10.9/100,000 among women (Ferlay et al., 2010). The majority (>90%) of adult kidney cancers are renal cell carcinomas (RCC; Eble et al., 2004).

Established risk factors for this cancer include cigarette smoking, hypertension, obesity, and von Hippel–Lindau syndrome, a rare condition caused by alternations or deletions in the *VHL* gene at chromosome 3p25. Suspected risk factors include diabetes mellitus and acquired cystic kidney disease (Scelo and Brennan, 2007). There is additionally some evidence for an inverse association between RCC risk and physical activity and moderate intake of alcohol (Chow and Devesa, 2008). While not normally considered an occupational cancer, studies have linked RCC to occupational exposure to styrene, gasoline or other petroleum products, asbestos, and organic solvents, particularly trichloroethylene (Mandel et al., 1995; Dosemeci et al., 1999; Bruning et al., 2003; Charbotel et al., 2006; Heck et al., 2010).

The capacity of an individual to activate or transform environmental toxins into less harmful intermediates, and the speed of metabolism, is important for modifying cancer risk. Several reviews have highlighted the genes associated with these processes and their relationship with the development of cancer (Hashibe et al., 2003; Nishikawa et al., 2004). Xenobiotic metabolizing enzymes activate (Phase I) substrates into more

reactive metabolites (cytochrome P-450 family) or play a detoxifying role (Phase II), which reduces the DNA reactivity of genotoxic species and increases excretion (*N*-acetyltransferases, NAD(P)H:quinone oxidoreductase I (*NQO1*), microsomal epoxide hydrolase (*mEH*), catechol-*O*-methyltransferase (*COMT*), uridine diphosphate-glucuronosyltransferase (*UGT*)). Both the Phase I and Phase II steps in toxin metabolism are influenced by genetic variation, affecting the rate at which carcinogens are metabolized and eliminated.

To date, there is a scarce literature examining polymorphisms in xenobiotic metabolizing genes in relation to RCCs. These studies found varying results, with some finding an association with *CYP1A1* (Schulz et al., 1997; Longuemaux et al., 1999; Farker et al., 2000; Semenza et al., 2001; Sasaki et al., 2004; Tanaka et al., 2007; Wiesenhutter et al., 2007; Smits et al., 2008). The purpose of this study was to examine the relationship between occupational exposures, common variation in metabolizing genes and kidney cancer.

MATERIALS AND METHODS

STUDY PARTICIPANTS

A hospital-based case–control study was conducted between 1998 and 2003 across seven centers in Central and Eastern Europe. The study centers were in the Czech Republic (Ceske, Prague, Olomouc, Brno), Poland (Lodz), Romania (Bucharest), and Russia (Moscow). In each center, investigators recruited a series of newly diagnosed cases of primary kidney cancer. Eligibility criteria included histologically confirmed disease (ICD-0-2 code C64) and residence in the study area for at least 1 year. Cases were recruited within 3 months of diagnosis. Additional details on the study have been reported elsewhere (Heck et al., 2010). All tumors underwent central review to confirm histology; the present analysis was limited to RCC.

In all centers, hospital-based controls were chosen among persons admitted to the same hospital as the cases with conditions unrelated to tobacco, including benign disorders, common infections, minor surgical conditions, eye conditions (except cataract or diabetic retinopathy), and common orthopedic diseases (except osteoporosis). No single disease made up greater than 20% of the control group (diseases of digestive system: 24%, musculoskeletal system/connective tissue: 12%, genitourinary system: 11%, skin and subcutaneous tissue: 10%, circulatory system: 9%, central nervous system: 9%, eye and ear: 8%, and other smaller categories combined: 17%). Some controls had been previously recruited from an earlier lung cancer case–control study (Boffetta et al., 2005). Controls were frequency matched to cases by sex, age (±3 years), center, referral (or of residence) area, and period of recruitment (±6 months).

Across centers, participation rates ranged from 90 to 99% among cases and 90 to 96% among controls. Written informed consent was obtained from all subjects prior to interview. Ethical approval was obtained from relevant review boards.

Trained interviewers administered a standardized questionnaire to participants which elicited information on personal medical history, family history of cancer, tobacco smoking, alcohol drinking, dietary and anthropometric factors, other lifestyle habits, and occupational history. The occupational interview consisted of a general questionnaire for each job, and for 16 prespecified jobs (toolmaker or machinist, motor vehicle mechanic, miner/quarryman, woodworker, painter, welder, insulation worker, meat worker or farmer, and the steel, coke manufacture, foundry, glass, tannery, chemical, and rubber industries) a specific questionnaire was also used. The general questionnaire intended to ascertain complete occupational history and additional information relevant to exposure assessment, including job titles, tasks, industries, starting and stopping dates, full-time/part-time status, working environments, and specific exposures.

The occupational exposure assessment was completed by local experts, including chemists, industrial hygienists, and occupational physicians, who had practical experience in industrial hygiene and took into account regional differences in use of materials, production processes, and prevention measures and changes in exposure patterns within and across jobs and industries over time for the different exposures. We attempted to standardize exposure assessment through yearly workshops and coding exercises. All participating study centers applied the same occupational questionnaires and the same protocol for expert assessment. We assessed inter-rater agreement, finding reasonably good agreement between experts (k between 0.53 and 0.64; Mannetje et al., 2003). Coders, blinded to case–control status, classified positions using the International Standard Classification of Occupation 1968 version (ISCO-68; International Labour Office, 1969) while industries were coded according to the Statistical Classification of Economic Activities of the European Community, 1999 version (NACE-99; Eurostat, 1999). Main effects results of the occupational analyses have been reported elsewhere (Karami et al., 2008; Heck et al., 2010; Moore et al., 2010; Boffetta et al., 2011).

Blood samples were collected and stored at −80°C prior to genotyping. All subjects in this study provided written informed consent. This study was approved by ethical review boards at the National Cancer Institute, the International Agency for Research on Cancer, and at each participating center.

GENOTYPING

Genes were selected based on their putative role in xenobiotic metabolism. Genotyping took place at IARC and at the National Cancer Institute's core genotyping facility. Genotyping was done using the 5′ nuclease assay (Taqman, Applied Biosystems) or Illumina GoldenGate® Oligo Pool All (OPA) assay, which was designed using publicly available sequencing information. Laboratory personnel were blinded to case–control status. Sequences of primers and probes were obtained from the SNP500 project (http://snp500cancer.nci.nih.gov/home.cfm). DNA from cases and controls were randomized on PCR plates and duplicate genotyping was performed on a randomly selected 10% of the samples for quality control. Call rates were similar for cases and controls, and exceeded 94% for both. All single nucleotide polymorphisms (SNPs) had a genotyping completion rate exceeding 99%. All duplicate quality control genotypes showed >99% concordance. Detailed methods for the genotyping can be found elsewhere (Karami et al., 2008; McKay et al., 2008).

We checked the SNPs included in this analysis against those used in a concurrent genome-wide association study being

Table 1 | Characteristics of the population.

	Cases		Controls		*p*-Value
	N	**%**	***N***	**%**	
SEX					
Male	523	59.8	1496	72.9	<0.0001
Female	351	40.2	557	27.1	
AGE					
<50	150	17.2	367	17.9	0.7
50–59	270	30.9	636	31.0	
60–69	280	32.0	677	33.0	
70+	174	19.9	373	19.9	
COUNTRY					
Romania	73	8.4	177	8.6	<0.0001
Poland	75	8.6	466	22.7	
Russia	260	29.8	797	38.8	
Czech Republic	466	53.3	613	29.9	
BODY MASS INDEX (BMI)					
<25	248	28.5	779	38.2	<0.0001
25+	623	71.5	1261	61.8	
HIGH BLOOD PRESSURE					
No	483	55.3	1272	62.0	0.0008
Yes	390	44.7	780	38.0	
ALCOHOL INTAKE (g/DAY, QUARTILES)					
0–518	231	31.7	429	23.8	<0.0001
519–1695	183	25.1	447	24.8	
1696–4229	170	23.3	462	25.6	
4230+	145	19.9	468	25.9	
TOBACCO (PACK-YEARS)					
None	409	46.8	729	35.5	<0.0001
1–19	192	22.0	512	24.9	
20+	273	31.2	812	39.6	

p-Values by chi-square testing.

conducted by our group, which used the Illumina 317K chip. Overall we found poor coverage of the genes of interest in this study with SNPs included in our GWAS, with most LD $r^2 < 0.05$. The exception was rs1056836, for which there was an r^2 of 0.77 with rs162330.

STATISTICAL ANALYSIS

Each polymorphism was tested in controls to ensure adherence to Hardy–Weinberg equilibrium (**Table 2**). SNPs exceeding Hardy–Weinberg equilibrium ($p < 0.01$) were excluded from the present analysis. For each SNP, we calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression after adjusting for potential confounders including country of residence, age (continuous), sex, blood pressure (high/low or normal), alcohol intake (g/day, quartile based upon the distribution in controls), and body mass index (<25, 25+). Analyses were conducted with SAS (Cary, NC, USA).

Haplotypes were calculated using fastPhase software (Scheet and Stephens, 2006). The fastPhase haplotypes were then used as covariates in the unconditional logistic regression model. We considered *NAT1*10* the highest risk genotype, as has been seen elsewhere, and additionally examined the risk associated with other genotypes (Bell et al., 1995; Cascorbi et al., 2001). Individuals homozygous for rapid *NAT2* acetylator alleles (*NAT2*4, NAT2*11A, NAT2*12A, NAT2*12B, NAT2*12C, NAT2*13*) were classified as rapid acetylator phenotype. Those homozygous for slow acetylator alleles were classified as slow acetylator phenotype and heterozygous individuals (one rapid and one slow *NAT2* allele) were classified as intermediate acetylator phenotype. We further examined the risk for specific haplotypes. In response to another investigation (Longuemaux et al., 1999), we examined whether any additional risk was conferred among *NAT2* slow acetylators who also had rarer variants of *CYP1A1*.

We conducted an exploratory analysis of exposure to occupational carcinogens among those with selected variants, and checked our findings in a case-only analysis. Stratified analyses were performed by exposure to gasoline, pesticides, and trichloroethylene. Given that tobacco use in some eastern European countries continues to rise (Bosetti et al., 2005; Perlman et al., 2007; Oh et al., 2010), we additionally examined joint effects with tobacco use.

Table 2 | Polymorphism in the xenometabolic gene and risk of kidney cancer (codominant model).

SNP amino acid change or gene region	rs Number	HWE	% homozygous wild type		OR (95% confidence interval) for risk with variant	SNP	rs Number	HWE	% homozygous wild type		OR (95% confidence interval) for risk with variant
			cases	controls					cases	controls	
NAT1 A40T	rs4986989	0.34	91.4	93.4	1.33 (0.97, 1.83)	NAT2Ex2 + 1750T > G	rs4646249	0.37	52.9	54.2	1.05 (0.90, 1.23)
NAT1 R187Q	rs4986782	0.11	96.6	98.0	1.61 (0.97, 2.65)	NAT2IVS1 + 3214G > C	rs7011792	0.37	37.2	35.2	0.94 (0.81, 1.09)
NAT1 C344T	rs4986988	0.64	91.3	92.8	1.17 (0.88, 1.57)	NAT2 Ex2 + 624A > G	rs721398	0.87	46.7	47.2	1.02 (0.88, 1.19)
NAT1 V149I	rs4987076	0.29	91.4	92.8	1.17 (0.87, 1.57)	NAT2 − 23931C > T	rs7006687	0.85	31.6	29.3	0.95 (0.82, 1.09)
NAT1 T1088A	rs1057126	0.68	64.5	64.7	1.01 (0.87, 1.17)	NAT2 5276 bp 3′ of STP A > C	rs12674710	0.41	68.0	73.3	1.16 (0.96, 1.40)
NAT1 C1095A	rs15561	0.61	55.3	55.5	1.02 (0.89, 1.17)	COMTV158M	rs4680	0.36	27.7	27.6	1.00 (0.89, 1.13)
NAT1 Ex2T > C NAT1	rs10888150	0.86	34.9	34.6	1.06 (0.92, 1.22)	CYP1A1 I462V	rs1048943	0.96	91.7	92.6	1.03 (0.76, 1.41)
IVS1 + 3238G > A NAT1	rs203943	0.45	83.2	82.3	0.94 (0.73, 1.21)	CYP1A1 T3801C	rs4646903	0.32	80.8	80.0	0.95 (0.78, 1.16)
IVS 1 + 4218A > G	rs13253389	0.62	41.4	43.0	1.07 (0.92, 1.24)	CYP1A2A164C	rs762551	0.86	47.5	46.2	0.97 (0.86, 1.10)
NAT1 IVS1 − 1014T > A	rs4921880	0.68	59.9	57.9	0.93 (0.78, 1.10)	CYP1A2G3858A	rs2069514	0.62	95.9	96.5	1.10 (0.72, 1.69)
NAT1 IVS1 − 2978A > G	rs6586714	0.42	71.7	73.3	1.13 (0.92, 1.38)	CYP1A2N516N	rs2470890	0.46	39.8	37.4	0.93 (0.83, 1.06)
NAT1 IVS2 + 312T > C	rs7003890	0.34	30.5	26.6	0.95 (0.82, 1.09)	CYP1B1 V432L	rs1056836	0.25	32.1	35.9	1.13 (1.01, 1.27)
NAT1 IVS1 + 385A > G	rs7017402	0.68	79.0	79.5	1.04 (0.83, 1.30)	CYP1B1 N453S	rs1800440	0.27	73.1	70.1	0.91 (0.78, 1.07)
NAT1 IVS1 − 3738T > C	rs9325827	0.73	72.4	72.2	0.95 (0.78, 1.17)	CYP2A6 L160H	rs1801272	0.65	96.0	96.6	1.07 (0.67, 1.71)
NAT1 Ex3 + 1010G > A	rs9650592	0.97	80.2	78.8	0.93 (0.74, 1.17)	CYP2C9 R430C	rs1799853	0.58	86.2	86.3	1.05 (0.86, 1.28)
NAT1 − 27893G > A	rs11778588	0.57	87.1	85.6	0.92 (0.69, 1.21)	CYP2C9 I359L	rs1057910	0.58	80.0	79.3	1.03 (0.82, 1.29)
NAT1 − 23972T > A	rs4921877	0.42	54.6	56.5	1.06 (0.91, 1.25)	CYP2E1 G1293C	rs3813867	0.79	94.8	95.0	1.07 (0.74, 1.56)
NAT1 8827 bp 3′ of STP C > G	rs7829368	0.79	47.2	45.3	0.97 (0.83, 1.13)	CYP2E1 G71T	rs6413420	0.22	90.3	90.4	0.98 (0.74, 1.28)
NAT1 − 28011A > G	rs7823976	0.57	33.8	32.0	0.95 (0.82, 1.09)	CYP3A4 A392G	rs2740574	0.54	93.4	92.6	0.92 (0.66, 1.27)
NAT2I114T	rs1801280	0.14	33.9	31.2	0.94 (0.83, 1.06)	MEH H139R	rs2234922	0.21	64.2	61.5	0.89 (0.76, 1.03)
NAT2 C481T	rs799929	0.09	36.0	33.7	0.92 (0.82, 1.04)	MEHY113H	rs1051740	0.90	43.6	45.2	1.01 (0.89, 1.15)
NAT2R197Q	rs1799930	0.63	47.9	48.3	1.01 (0.89, 1.15)	NQ01 P187S	rs1800566	0.64	64.0	66.4	1.13 (0.98, 1.31)
NAT2 L268R	rs1208	0.08	35.1	31.8	0.92 (0.81, 1.04)	NQ01 R139W	rs4986998	0.71	94.3	94.8	0.99 (0.69, 1.41)
NAT2 C282T	rs1041983	0.55	45.4	45.4	0.98 (0.86, 1.11)	NQ01 − 3617C > G	rs2917666	0.26	43.3	47.1	1.15 (0.96, 1.37)
NAT2 G286E	rs1799931	0.87	95.8	95.6	0.89 (0.59, 1.33)	NQ01 IVS1 + 1116T > C	rs2917669	0.71	74.5	75.3	1.09 (0.94, 1.27)
NAT2IVS1 − 1799A > G	rs1961456	0.62	52.7	53.2	1.04 (0.89, 1.22)	NQ01 − 4069G > A	rs1469908	0.31	33.6	38.2	1.09 (0.94, 1.26)
NAT2IVS1 − 3041T > C	rs2410556	0.14	77.8	75.6	0.82 (0.66, 1.02)	UGT1A7N12	rs17868323	0.30	40.7	40.0	0.99 (0.87, 1.12)
NAT2 Ex2G > C	rs4271002	0.64	78.5	75.8	0.85 (0.68, 1.06)						

**OR (95% CI) by unconditional logistic regression, controlling for age, sex, study center, blood pressure, BMI, pack-years of smoking, and alcohol use. Hardy–Weinberg equilibrium (HWE) as measured in the control population.*

Table 3 | Odds ratios (OR), 95% confidence intervals (95%CI) for the associations of polymorphisms in NAT and renal cell cancer risk.

	Case *N*	Control *N*	OR (95% CI)
NAT1			
Rapid	572	1341	Referent
Intermediate	253	626	1.03 (0.85, 1.26)
Slow	30	58	1.12 (0.88, 1.43)
NAT2			
Rapid	54	108	Referent
Intermediate	310	731	0.76 (0.51, 1.14)
Slow	491	1172	0.82 (0.69, 1.01)

OR (95% CI) by unconditional logistic regression, controlling for age, sex, study center, high blood pressure, body mass index, pack-years of cigarette smoking, and alcohol intake.

RESULTS

Of the 954 eligible kidney cancer cases who provided genomic DNA, 80 were excluded due to having histology other than renal cell carcinoma. The 874 cases in the current analysis had clear cell carcinoma ($N = 792$, 90.6%), papillary ($N = 61$, 7.0%), chromophobe ($N = 19$, 2.2%), and two (<1%) cases of oncocytic neoplasm.

The population was described in **Table 1**. The largest proportion of participants was from the Czech Republic. Cases were more likely to be overweight or obese and were more likely to have high blood pressure, in comparison to controls. Controls had greater tobacco use than cases, with the greatest person-years of tobacco use observed in Russia and Poland (data not shown). After elimination of three SNPs that were out of Hardy–Weinberg equilibrium, 56 SNPs remained (**Table 2**). In the main effects analysis, *CYP1B1V432L* was associated with RCC risk ($p = 0.03$). Examining this variant, we additionally tested for heterogeneity of results. We did observe different associations by country of residence ($p = < 0.0001$). Results of a random effects model were similar to the fixed effects regression (OR = 1.13, 95% CI 1.01, 1.27). After adjustment for multiple comparisons via Bonferroni, it did not remain significant.

In haplotype analyses, we did not observe any association between RCC and *NAT1*10* or with *NAT2* slow acetylation (**Table 3**). We were not able to replicate the findings of Longuemaux et al. (1999) who observed additional risk among *NAT2* slow acetylators with rarer *CYP1A1* variants (OR = 1.57, 95%CI 0.96, 2.56). After stratifying by occupational exposures, we did not observe a greater risk for RCC among *NAT1*10* or *NAT2* slow acetylators who were tobacco users or occupationally exposed to chemical agents (data not shown), nor did we observe associations when examining risk in the case-only analysis.

DISCUSSION

To our knowledge, this is the largest study yet conducted of xenometabolic genes in relation to RCC. In this Central and Eastern European population, we observed no clear associations between RCC and genetic variation in the xenometabolic genes. It is likely that if these variants had a true association with disease, we would have observed differing effects between smokers and non-smokers. Although this study's controls had high rates of smoking, making such a differential effect difficult to observe (Heck et al., 2010), we also did not see associations in the case-only analysis.

To our knowledge, there have been two other studies examining *NAT2* slow acetylation and RCC. One study (N cases = 115) found a strong association between *NAT2* genotype and RCC (OR = 1.8; Semenza et al., 2001). The other (N cases = 73) found no independent association with slow acetylator genotype alone (OR = 1.1), although a greater risk was seen among persons who also had certain *CYP1A1* variants (Longuemaux et al., 1999). We were not able to replicate these results. Differing findings are likely due to chance.

The *CYP1B1*3* variant was common, with 47.0% of total samples heterozygous C/G and 18.2% homozygous G/G. This genotype is associated with an amino acid substitution from leucine to valine, with higher catalytic activity for Val432 variants than Leu432 variants, potentially causing a differential susceptibility toward tobacco-related cancers. A small study in Japan reported a 50% increase in RCC among heterozygous C/G participants, and an over twofold risk among homozygous G/G participants (Sasaki et al., 2004). This variant has been tested in relation to several other cancers and health conditions. The literature is inconsistent as to whether there is a relationship between this variant and lung cancer (Wenzlaff et al., 2005; Cote et al., 2007; Shah et al., 2008), while no association has been seen with cancers of the ovary or head and neck (Cecchin et al., 2004; Singh et al., 2008).

One study reported higher prevalence of *NQO1* variants among RCC patients (Schulz et al., 1997). In our population, there was a marginally greater prevalence among cases of polymorphisms of *NQO1* codon 187 ($p = 0.07$), while the distribution of all other *NQO1* SNPs did not differ between cases and controls.

If genetic susceptibility to renal cancer is mediated through metabolic gene polymorphisms, it is possible that combinations of genotypes may be a more meaningful predictor of disease risk than examining single loci genotype, and this study lacked power to do detailed analyses. A strength of the study is the expected genetic homogeneity of the eastern European population, lowering the likelihood of bias from population stratification (Wacholder et al., 2000). Nonetheless, we did observe heterogeneity in the results. Hospital-based controls in our study could potentially cause selection bias if specific genetic variants were related to hospitalization. However, controls with a variety of medical conditions were recruited into the study, lessening the likelihood of such a bias.

In conclusion, no clear associations were observed between RCC and several polymorphisms related to xenobiotic metabolism.

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